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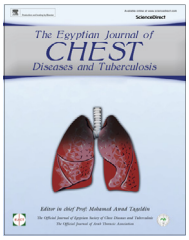

REVIEW

Does serum 25 hydroxy vitamin D level play a role in COPD?

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KEYWORDS

Vitamin D, LL-37;
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Abstract It has been recognized that, in addition to its classical function, vitamin D modulates a variety of processes and regulatory systems including host defense, inflammation, and immunity. Some authors concluded that there is strong relation between vitamin D serum level and lung functions but others concluded that there is no relation between them.

Aim of the work: To study the role of serum level of 25 hydroxy-vitamin D in COPD patients, also, assess the serum level of vitamin D dependent LL-37 and IFNγ and to study the link between the three parameters and pulmonary functions in these patients.

Subjects and methods: This study was conducted on 40 persons who were divided into GI, 10 controls and GII, 30 COPD patients. FEV1, serum levels of 25 hydroxy vitamin D, LL-37 and IFNγ were measured.

Results: Serum levels of 25 hydroxy vitamin D and LL-37 were significantly decreased in GII as compared to GI while serum level of IFNγ was significantly increased in GII as compared to GI and there was a significant positive correlation between vitamin D level and FEV1 and LL-37 level while there was a negative correlation between it and IFNγ level.

Conclusion: Vitamin D level affects pulmonary function in COPD through its effect on LL-37 and IFNγ serum level.

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Introduction

The role of vitamin D in calcium and bone homeostasis is well described. In the last years, it has been recognized that, in addition to its classical function, vitamin D modulates a variety of processes and regulatory systems including host defense, inflammation, and immunity and repair, especially patients with lung diseases often have low vitamin D serum level. Epidemiological data indicated that low serum level of vitamin D is associated with impaired pulmonary function, increased incidence of inflammatory infectious or neoplastic diseases [1]. Recently, the connection between vitamin D status and COPD has attracted attention [2]. Some authors concluded that there was a strong relationship between serum level of vitamin D and lung functions. In contrast, others did not find any relation between them [3]. Cathelicidin LL-37 is the only member of the cathelicidin family of host defense peptides that is expressed in humans. It is a linear 37 amino acid peptide produced from the C-terminus of hCAP18 precursor protein by a proteolytic cleavage [4]. LL-37 is produced by phagocytic leucocytes and other cells, it is a major constituent of zurophilic granules of neutrophils, it has direct antimicrobial action and diverse immuno-modulatory properties [5,6]. Importantly, the production of LL-37 in human primary monocytes in response to infection is dependent on 1.25 vit D3 either exogenously supplemented in ex vivo systems or naturally present in human serum [7]. In addition to the widely recognized role of 1.25 vit D3 in antimicrobial immunity, it is also known to have anti-inflammatory activity, suppressing the intentions of TNFα, IFNγ and IL12 p40 [8]. Thus, the recently established role of 1.25 vit D3 in LL-37 induction further reinforces the notion that LL-37, may function in the context of "non classical", non inflammatory responses to infection. Possible contributions of LL-37 to the anti-inflammatory activity of the 1.25 vit D3 system remain to be investigated [9].

Aim of the work

Is to study the role of serum level of 25 hydroxy-vitamin D in COPD patients through the assessment of the serum levels of vitamin D dependent LL-37 and IFNγ and to study the link between the three parameters and pulmonary functions in these patients.

Patients and methods

This work included 40 persons collected from the outpatients chest clinic in the Tanta University hospitals in the period from February to May 2013 and were divided into two groups.

Group I: Included 10 apparently healthy non smoker volunteers, 7 males and 3 females, and their mean ages were 40 ± 3 years.

Group II: Included 30 COPD patients, 26 males and 4 females and their mean ages were 52 ± 2.5 years.

COPD patients should fulfill the following criteria

Patients were non smokers or exsmokers (for at least 1 year) and had a history of COPD. FEV1/FVC < 70%, % of recovery after bronchodilator therapy is <15%, X-ray chest PA view develops hyperinflation and X-ray chest "lateral view" showed retrosternal airspace >2.5 cm if measured form anterior border of ascending aorta to posterior border of manubrium sterni.

Exclusion criteria were

If patients had bronchial asthma, other chronic lung diseases or history of upper or lower respiratory tract infections in the last month, history of vitamin D supplements within 1 month and acute exacerbation of COPD.

All persons were subjected to full history taking and full clinical examination. Plain chest X ray (PA and lateral views),

Table 1 Mean, standard deviation and statistical analysis of spirometeric data in GI and GII.

	GI	GII	*t* Test	*p* Value
FVC	96.76 ± 1.73	70.55 ± 6.48	12.632	0.001
FEV1	97.60 ± 1.78	40.83 ± 6.35	27.528	0.001
FEV1/FVC	100.9 ± 2.95	57.61 ± 4.34	29.230	0.001
PEFR	96.31 ± 2.10	61.25 ± 6.85	15.360	0.001
FEF 25–75%	98.07 ± 1.56	61.35 ± 6.71	14.528	0.001

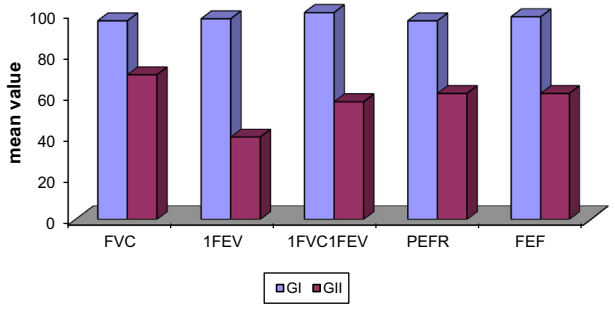

Figure 1 Mean, standard deviation and statistical analysis of spirometeric data in GI and GII.

Table 2 Mean, standard deviation and statistical analysis of serum level of 25-hydroxy vitamin D nmol/l in GI and GII.

	GI	GII	*t* Test	*p* Value
Serum level of 25-hydroxy vitamin D	181.32 ± 4.48	64.12 ± 3.61	62.33	0.001

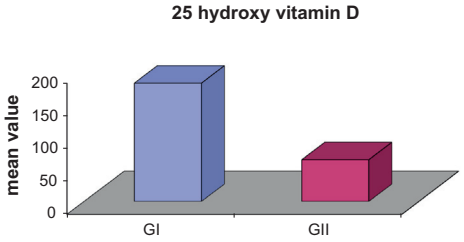

Figure 2 Mean, standard deviation and statistical analysis of serum level of 25 hydroxy vitamin D nmol/l in GI and GII.

spirometry, and venous blood samples were taken for measurement of serum levels of 25 hydroxy vitamin D, LL-37 and IFNγ. Measurement of 25 hydroxy vitamin D (expressed as nmol/l) "using immunodiagnostic Enzyme-immuno-Assay (EIA)" developed by immunodiagnostic bensheim and biomedical, wein, Australia catalog No. 02082005 25 OHvit D6.DOC. LL-37 plasma level (expressed as ng/ml) was determined with ELISA kit (HK 321 humanLL-37 ELISA kit, Hycult biotechnology uden. INFγ (expressed as pg/ml) was detected using the ELISA kit (Max Discovery TM human interferon Gamma Bioscientific, USA, assay). Statistical presentation and analysis of the present study were conducted using the mean, standard deviation and person correlation test by SPSS. Written consent was taken from all persons taking part in this study.

Results

Table 1 and Fig. 1 showed that mean values of actual value of FEV1/FVC and percent of predicted FVC, FEV1, PEFR and FEF 25–75% in group I was 100.9 ± 2.95, 96.76 ± 1.73, 97.6 ± 1.78, 96.3 ± 12.1 and 98.07 ± 1.56 respectively. The mean values of actual value of FEV1/FVC and percent of predicted FVC, FEV1, PEFR and FEF 25–75% was 57.6 ± 14.34, 7.55 ± 6.48, 40.83 ± 6.35, 61.31 ± 6.85 and 61.35 ± 6.71 respectively. There was a significant decrease in all parameters in group II as compared to group I ($p < 0.05$). Table 2 and Fig. 2 showed that mean values of serum level of 25 hydroxy vitamin D in groups I and II were 181.32 ± 4.48 and 64.12 ± 3.61 respectively. There was a significant decrease in group II as compared to group I ($p < 0.05$). Table 3 and Fig. 3 showed that mean values of serum level of LL-37 in groups I and II were 97.14 ± 1.8 and 25.36 ± 3.07 ng/ml respectively. There was a significant decrease in group II as compared to group I ($p < 0.05$). Table 4 and Fig. 4 showed that mean values of serum level of IFNγ in groups I and II were 14.35 ± 1.31 and 63.65 ± 7.95 pg/ml respectively. There was a significant increase in group II as compared to group I ($p < 0.05$). Table 5 and Figs. 5–7 showed that there was a significant positive correlation between serum level of 25 hydroxy vitamin D and both FEV1 and serum level of LL-37 but there was a significant negative correlation between serum level of 25 hydroxy vitamin D and serum level of IFNγ.

Discussion

In this study, there was vitamin D deficiency in COPD group and FEV1 had a significant positive correlation to 25 hydroxy vitamin D level. Louise et al. concluded that COPD was associated with an increased risk of vitamin D deficiency and important disease characteristics were significantly related to 25 hydroxy vitamin D levels especially FEV1 [10]. Black et al. found a dose response relationship between 25 hydroxy

Table 3 Mean, standard deviation and statistical analysis of serum level of LL-37 (ng/ml) in GI and GII.

	GI	GII	*t* Test	*p* Value
Serum level of LL-37	97.14 ± 1.80	25.36 ± 3.07	70.93	0.001

Table 4 Mean, standard deviation and statistical analysis of serum level of IFNγ (pg/ml) in GI and GII.

	GI	GII	*t* Test	*p* Value
Serum level of IFNγ	14.35 ± 1.31	63.65 ± 7.95	19.35	0.001

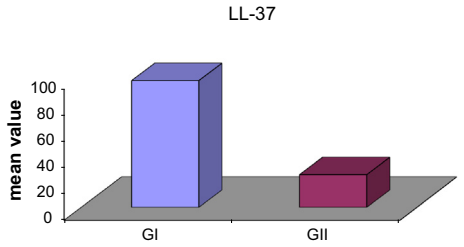

Figure 3 Mean, standard deviation and statistical analysis of serum level of LL-37(ng/ml) in GI and GII.

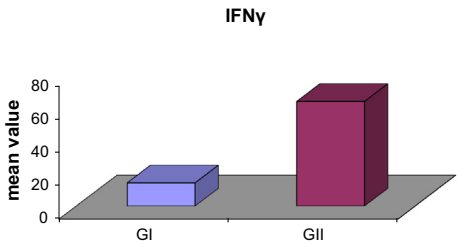

Figure 4 Mean, standard deviation and statistical analysis of serum level of IFNγ (pg/ml) in GI and GII.

Table 5 Correlation between serum level of 25 hydroxy vitamin D and serum levels of LL-37, IFNγ and FEV1.

	25-Hydroxy vitamin D	
	r	*p*
Serum level of LL-37	0.863	0.001
Serum level of IFNγ	−0.745	0.001
FEV1	0.896	0.001

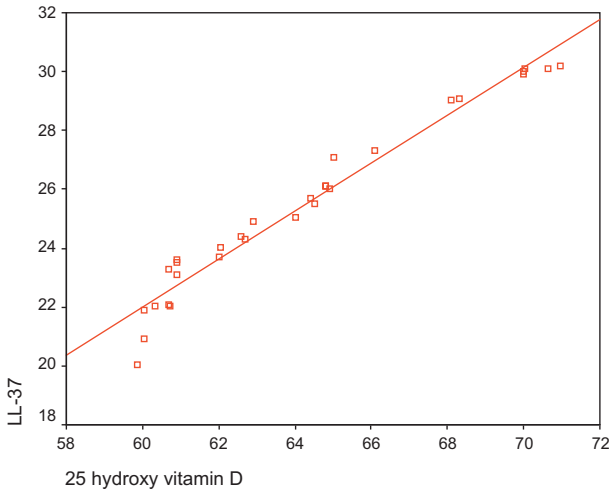

Figure 5 Correlation between serum level of 25 hydroxy vitamin D and serum level of LL-37.

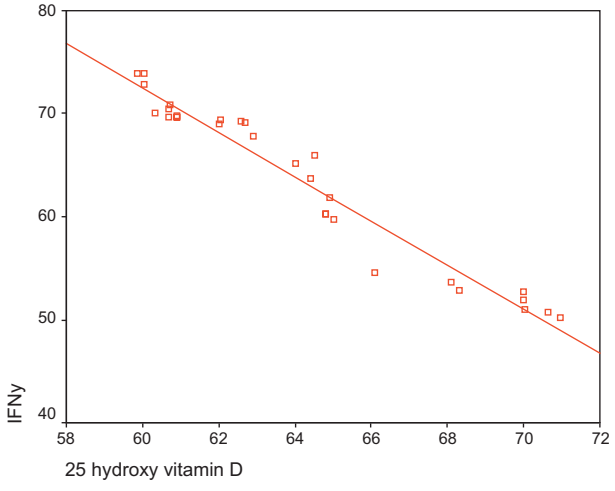

Figure 6 Correlation between serum level of 25 hydroxy vitamin D and serum level of IFNγ.

vitamin D and both FEV1 and FVC [2]. Janssens et al. showed a nearly identical relationship between airway obstruction and vitamin D level [11]. A similar association between 25 hydroxy vitamin D and FEV1, has been reported in adults with asthma [12].

Vitamin D has several functions, in addition to bone mineralization, vitamin D has been shown to be an important regulator of both elements of the immune system, has a role in

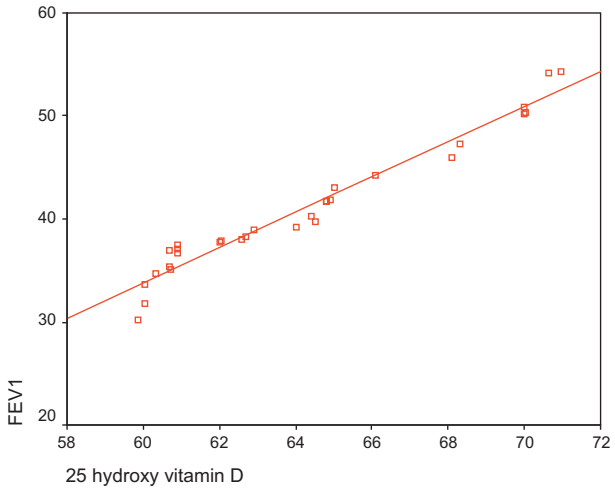

Figure 7 Correlation between serum level of 25 hydroxy vitamin D and FEV1.

dendritic cell maturation [13], T cell activation and proliferation [14] and Th1 T cell development [15], decrease the susceptibility to respiratory infections, decrease the expression of pro-inflammatory cytokines and chemokines [16]. Vitamin D has been shown to directly affect processes involved in tissue remodeling such as fibroblast proliferation and collagen synthesis and modulation of matrix metalloproteinase levels [17]. Undiagnosed osteoporosis leading to vertebral compression may lead to loss in height, reduced rib cage mobility and decline in pulmonary function [18]. Patients with COPD should be considered at high risk of vitamin D insufficiency because of reduction of outdoor activity, increased glucocorticoids induced catabolism, impaired activation as a consequence of renal dysfunction, and a lower storage capacity in muscle and fat due to wasting [19]. Franco et al., concluded that severity of COPD was related to low vitamin D level [20]. In contrast, Bjerk et al., found that in severe COPD patients, 2000 iu of daily vitamin D for 6 weeks increased 25 hydroxy vitamin D level widely considered as normal, however, compared with placebo, vitamin D supplementation has no discernible effect on short physical performance Battery scorer and St. Georges Respiratory question the naive score [21]. 1,25 dihydroxy vitamin D is essential for induction of LL-37 through intracellular vitamin D receptor as well as steroid receptor co-activator and histone acetylation [22]. In our study, there was a decrease in vitamin D level and LL-37 level which had several actions, microbiocidal activity, suppressing the induction of TNFα, IFN γ and IL12p 40, inhibits formation of pseudomonas aeriginosa biofilms, suppress of LPS-induced production of inflammatory cytokines, neutrophils apoptosis which may play a role in pathogenesis of COPD [23,9,24]. Lemire concluded that active vitamin D metabolite 1,25 dihydroxy vitamin D3 promotes many of its actions through interaction with specific intra cellular receptor located in monocytes and activated lymphocytes which leads to the concept that vitamin has a role in immune system. Sterol inhibits lymphocyte proliferation and immunoglobulin production in a dose-dependent fashion, at a molecular level q,25-D3 inhibits the accumulation of MRNA for IL-2, IFNγ and GM-CSF [25] so, this study concluded that vitamin D deficiency leads to reduction in lung functions in

COPD patients through its effect on serum levels of LL-37 and IFNγ and recommended that serum level of 25 hydroxy vitamin D can be used in monitoring the severity of COPD and vitamin D supplement may be beneficial in COPD patients.

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